Randomized, Placebo-Controlled Trial of HA-1A, a Human Monoclonal Antibody to Endotoxin, in Children with Meningococcal Septic Shock

Bert Derkx, Janet Wittes, Richard McCloskey, and the European Pediatric Meningococcal Septic Shock Trial Study Group*

From the Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Department of Pediatrics, Amsterdam, the Netherlands; Statistics Collaborative, Inc., Washington, D.C., USA; and Centocor, Inc., Malvern, Pennsylvania, USA

Meningococcal septic shock has a rapid onset and characteristic skin hemorrhages that allow bedside diagnosis. Initial plasma endotoxin levels are high and correlate closely with clinical outcome. In a double-blind, randomized, placebo-controlled trial (planned, $n = 270$; actual, $n = 269$), we compared the effectiveness of HA-1A (6 mg/kg of body weight iv; maximum, 100 mg), a human monoclonal antibody to endotoxin, and placebo in reducing the 28-day all-cause mortality rate among children with a presumptive clinical diagnosis of meningococcal septic shock. Treatment groups were well balanced for baseline characteristics and prespecified prognostic variables. In this trial no significant benefit of HA-1A could be demonstrated. The 28-day mortality rates in the intention-to-treat analysis were as follows: placebo, 28%; HA-1A, 18%; reduction in mortality, 33% ($P = .11$, per Fisher's exact test, two-tailed; odds ratio = 0.59; 95% confidence interval for the difference, 0.31–1.05). All patients tolerated HA-1A well, and no antibodies to HA-1A were detected.

Fulminant meningococcal septic shock (MSS) remains a highly fatal disease despite the continuing advances in supportive care [1]. Endotoxin, the lipopolysaccharide (LPS) component of the gram-negative bacterial cell wall, is considered to be the most important bacterial factor in the pathogenesis of systemic meningococcal infections. In patients with *Neisseria meningitidis* bacteremia, initial plasma endotoxin levels correlate closely with morbidity and mortality, and these levels are often several logs higher than commonly observed in other forms of gram-negative septicemia [2–4]. The endotoxin levels are, furthermore, quantitatively associated with key mediators contributing to the host's inflammatory response [4, 5]. The toxic moiety of endotoxin is lipid A, which is relatively well conserved among different gram-negative bacteria [6, 7].

The assumed central role of endotoxin in gram-negative sepsis has led to the investigation of different antibodies directed against the lipid A moiety of endotoxin in several clinical trials. Increased survival has been demonstrated among gram-negative bacteremic patients with septic shock treated with sera obtained from individuals immunized with injections of an *Escherichia coli* mutant (J5) [8]; however, a study of children with severe infectious purpura (mainly due to meningococcemia) found that antiserum to J5 did not significantly alter the clinical course or mortality [9].

Several randomized clinical trials have been performed to study the efficacy of two monoclonal antibodies: E5, a murine IgM, and HA-1A, a human IgM. In the first E5 trial, antibody treatment appeared to augment the survival rate among patients with gram-negative sepsis who were not in shock [10]. This finding was not confirmed in a second study, although a trend toward improved survival rates among treated patients with major organ failure was observed [11]. In both trials the subgroup effects were not shown to differ in magnitude from the effect in the remainder of the patients in the trial.

Two large clinical trials with HA-1A have been published. The first study showed no overall benefit of HA-1A, but significant improvement in the survival rate was observed in a subgroup of patients with gram-negative bacteremia and shock [12]. Again, the effect in this subgroup did not differ significantly from the effect in the other subgroups. A second trial that also showed no overall clinical benefit of HA-1A was discontinued at the first interim analysis because of a nonsignificant survival disadvantage among patients without gram-negative bacteremia [13]. Although these results do not provide clear evidence of increased survival among patients with sepsis, they do not preclude the possibility that anti-endotoxin therapy might be beneficial for certain patients with gram-negative septicemia. The heterogeneity of etiologic organisms and patients with presumed sepsis and time of administration of the study drug may help to explain these disappointing results.

MSS is an ideal model for the study of immunotherapy in sepsis because its rapid onset and characteristic skin hemorrhages allow bedside diagnosis. The aims of this study were to evaluate the efficacy of a single dose of HA-1A in children with MSS and in patient subgroups defined by *N. meningitidis* culture and antigen status. The secondary objective was to assess the safety of HA-1A.

Received 19 May 1998; revised 22 October 1998.

Dr. McCloskey is a full-time employee of Centocor, Inc. Dr. Wittes had a contract from Centocor, Inc., for the analytic plan and performance of the final analysis.

Grant support: Centocor, Inc.

* The institutions and investigators participating in the study are listed in the Appendix.

Reprints or correspondence: H. H. F. Derkx, Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Department of Pediatrics, P.O. Box 22700, 1100 DE Amsterdam, the Netherlands (h.h.derkx@amc.uva.nl).

Clinical Infectious Diseases 1999;28:770–7

1058–4838/99/2804–0016$03.00

17. Capeding RMZ, Nohynek H, Ruutu P, Leinonen M. Evaluation of a new tube latex agglutination test for detection of type-specific pneumococcal antigens in urine. J Clin Microbiol 1991:29:1818–21.
18. Coonrod JD, Rytko-Bauer. Latex agglutination in the diagnosis of pneumococcal infection. J Clin Microbiol 1976;4:168–74.
19. Tugwell P, Greenwood BM. Pneumococcal antigen in lobar pneumonia. J Clin Pathol 1975;28:118–23.
20. Severin WPJ. Latex agglutination in the diagnosis of meningococcal meningitis. J Clin Pathol 1972;25:1079–82.
21. Newman RB, Stevens RW, Gaafar HA. Latex agglutination test for the diagnosis of *Haemophilus influenzae* meningitis. J Lab Clin Med 1970; 76:107–13.
22. Lim PL, Choy WF. A spectrophotometric method for evaluating a latex agglutination assay of *Salmonella typhi* lipopolysaccharide. J Immunol Methods 1988;115:269–74.
23. Kaldor J, Asznowicz R, Buist DGP. Latex agglutination in diagnosis of bacterial infections, with special reference to patients with meningitis and septicemia. Am J Clin Pathol 1977;68:284–9.
24. Ramsey BW, Marcuse EK, Foy HM, et al. Use of bacterial antigen detection in the diagnosis of pediatric lower respiratory tract infections. Pediatrics 1986;78:1–9.
25. Requejo HIZ, Nascimento CMPC, Fahrat CK. Comparison of counterimmunoelectrophoresis, latex agglutination and bacterial culture for the diagnosis of bacterial meningitis using urine, serum and cerebrospinal fluid samples. Braz J Med Biol Res 1992:25:357–67.
26. Whittle HC, Tugwell P, Egler LJ, Greenwood BM. Rapid bacteriological diagnosis of pyogenic meningitis by latex agglutination. Lancet 1974; 2:619–21.
27. Smith LP, Hunter KW, Hemming VG, Fischer GW. Improved detection of bacterial antigens by latex agglutination after rapid extraction from body fluids. J Clin Microbiol 1984;20:981–4.
28. Weinberg GA, Storch GA. Preparation of urine samples for use in commercial latex agglutination tests for bacterial antigens. J Clin Microbiol 1985;21:899–901.
29. Shann F, Gratten M, Germer S, Linnemann V, Hazlett D, Payne R. Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. Lancet 1984;2:537–41.
30. Rodriguez Barradas MC, Musher DM, Hamill RJ, Dowell M, Bagwell JT, Sanders CV. Unusual manifestations of pneumococcal infection in human immunodeficiency virus–infected individuals: the past revisited. Clin Infect Dis 1992;14:192–9.
31. Dobroszycki J, Abadi J, Lambert G, Beenhouwer DO, Truong TH, Wiznia AA. Testicular abscess due to *Streptococcus pneumoniae* in an infant with human immunodeficiency virus infection. Clin Infect Dis 1997; 24:84–5.
32. Cruickshank R. The urinary excretion of pneumococcus polysaccharide in lobar pneumonia. J Pathol Bacteriol 1938;46:67–75.
33. Pepper DS. The urinary excretion of S substance in lobar pneumonia. Yale J Biol Med 1934;7:13–21.
34. Pichichero ME. Immunological paralysis to pneumococcal polysaccharide in man. Lancet 1985;2:468–71.
35. Lund E, Henrichsen J. Laboratory diagnosis, serology and epidemiology of *Streptococcus pneumoniae*. In: Bergan T, Norris JR, eds. Methods in microbiology. New York: Academic Press, 1978:241–62.
36. Sottile MI, Rytel MW. Application of counterimmunoelectrophoresis in the identification of *Streptococcus pneumoniae* in clinical isolates. J Clin Microbiol 1975;2:173–7.
37. Coonrod JD, Rytel MW. Detection of type-specific pneumococcal antigens by counterimmunoelectrophoresis. I. Methodology and immunologic properties of pneumococcal antigens. J Lab Clin Med 1973;81:770–7.
38. Murphy TV, Clements JF, Granoff DM. Excretion of *Haemophilus influenzae* type b polysaccharide antigen in urine of healthy nasopharyngeal carriers. Pediatr Res 1989;26:491–5.
39. Bullowa JGM. The reliability of sputum typing and its relation to serum therapy. JAMA 1935;105:1512–8.
40. Page MI, Lunn JS. Pneumococcal serotypes associated with acute pneumonia. Am J Epidemiol 1973;98:255–61.
41. Brandileone MCdC, Vieira VSD, Zanella CR, et al. Distribution of serotypes of *Streptococcus pneumoniae* isolated from invasive infections over a 16-year period in the Greater Sao Paulo Area, Brazil. J Clin Microbiol 1995;33:2789–91.
42. Austrian R, Howie VM, Ploussard JH. The bacteriology of pneumococcal otitis media. Johns Hopkins Medical Journal 1977;141:104–11.
43. El-Refaie M, Tait R, Dulake C, Dische FE. Pneumococcal antigen in pneumonia. A postmortem study with the histological and bacteriological findings. Postgrad Med J 1976;52:497–500.
44. Kenny GE, Wentworth BB, Beasley RP, Foy HM. Correlation of circulating capsular polysaccharide with bacteremia in pneumococcal pneumonia. Infect Immun 1972;6:431–7.
45. Leinonen M. Detection of pneumococcal capsular polysaccharide antigen by latex agglutination, counterimmunoelectrophoresis, and radioimmunoassay in middle ear exudates in acute otitis media. J Clin Microbiol 1980;11:135–40.

Methods

Protocol

During a period of 4 years (April 1991 to May 1995), 269 patients with clinical evidence supporting a presumptive clinical diagnosis of fulminant MSS were enrolled in the trial. A patient was eligible for the study if the referring physician agreed to provide aggressive, supportive care and if the child (1) had petechiae (pinpoint hemorrhage, <2 mm) and/or purpura (palpable or nonpalpable hemorrhage(s), ≥2 mm), (2) was older than 3 months but less than 18 years, and (3) had persistent hypotension requiring aggressive therapy within 12 hours before enrollment. Hypotension was defined as systolic blood pressure of <75 mm Hg for children aged 3–12 months, <80 mm Hg for children aged 1–5 years, <85 mm Hg for children aged 6–12 years, and <100 mm Hg for those aged >12 years.

A nonhypotensive child was eligible if there was evidence of systemic toxicity or poor end-organ perfusion, defined by at least two of the following criteria, within 24 hours of enrollment: (1) unexplained metabolic acidosis, defined as a pH of ≤7.3, a base deficit of ≥5, or a plasma lactate level of >2 mmol/L; (2) arterial hypoxia, defined by a P_{O_2} (partial pressure of oxygen) of ≤75 mm Hg, a P_{O_2}/F_{IO_2} (fraction of inspired oxygen) ratio of <250, or T_{CO_2} (total carbon dioxide, saturated) of ≤96% in patients without overt pulmonary disease as the cause; (3) acute renal failure, defined as oliguria with a urine output of <0.5 mL/(kg · h) for at least 1 hour despite acute fluid volume loading or evidence of adequate intravascular volume and no renal disease; and (4) sudden deterioration of baseline mental status. Children participating in other investigational drug trials, those who had previously received a monoclonal antibody or intravenous immunoglobulin, pregnant girls, and children for whom there was a "do not resuscitate" order were excluded.

The institutional review boards and local research ethics committees of all participating centers approved the study protocol before enrollment began. Parents or legal guardians gave written consent after receiving oral and written information.

The primary objective of the trial was to study the efficacy of a single dose of HA-1A (6 mg/kg body weight [bw] iv; maximum, 100 mg) compared with that of placebo in reducing the 28-day all-cause mortality rate among children (aged >3 months and <18 years) admitted with a presumptive clinical diagnosis of MSS and in patient subgroups defined by *N. meningitidis* culture and antigen status. The secondary objective was to assess the safety of HA-1A.

The study was a double-blind, randomized, placebo-controlled, multicenter, fixed-sample-size trial with planned interim analysis after enrollment of ⅓ and ⅔ of the total number of patients (n = 270). Epidemiological data predicted a 30% mortality rate in the placebo group, and the expected 28-day all-cause mortality rates in the placebo and HA-1A groups were 30% and 15%, respectively. The calculated sample size of 270 patients provided 80% power for a two-sided α = 0.05 test of significance by means of Fisher's exact test [14]. The trial was designed with O'Brien-Fleming-Harrington sequential boundaries [15] to permit early termination of the study for reasons of overwhelming treatment efficacy. Under this plan, the overall two-sided significance of 0.05 was maintained by setting the significance level for the two interim analyses at 0.010 and 0.013 and setting the final significance level at 0.039.

An independent Safety and Efficacy Monitoring Committee assessed the results of the trial. The committee had the authority to recommend early termination of the trial if the difference in survival reached significance or if serious or unexplained side effects occurred. The analyses were performed on the "intention-to-treat" population. Secondary analyses included covariate-adjusted logistic regressions, subgroup analyses of the primary endpoint, and Kaplan-Meier survival analyses [16] comparing the placebo and HA-1A groups. Survival curves were tested with log-rank tests. The data were fit with use of a series of logistic regression models with 28-day mortality as the outcome. Treatment group and several baseline covariates including baseline log (endotoxin) were used as predictor variables.

As a part of the investigation of the properties of HA-1A, the following subgroups were analyzed: treated patients only, treated patients with a documented non–*N. meningitidis* cause of their initial presentation, treated patients with a positive *N. meningitidis* culture or a positive antigen test, treated patients with at least one *N. meningitidis*–positive culture (of blood, CSF, or a skin aspirate), and treated patients with at least one *N. meningitidis*–positive blood culture. The primary efficacy analyses were performed on each of these subgroups, as well as on 56-day mortality. Fisher's exact tests were used; because no interim analyses were performed on the 56-day endpoint, the significance level was set at 0.05.

Other nonmortality endpoints included the event rate for the following sequelae categories separately and as a composite: amputation, skin grafts, severe neurological sequelae, deafness, blindness, and pericarditis/myocarditis. The analytic plan identified several secondary variables to be analyzed in the primary population and the subgroups of interest, such as change in hematologic and biochemical parameters from baseline, including endotoxin level. Statistical analyses were performed with use of SAS software, version 6.08 [17]. Power calculations were performed with use of PASS 6.0 [18].

Assignment

Children were randomly assigned by center in blocks of two or four to receive either HA-1A or placebo. Treatment was assigned at the individual patient level. Within each center each child received a consecutive enrollment number when eligibility for the study was confirmed. Twenty-six centers with pediatric intensive care facilities in The Netherlands, Great Britain, France, Spain, and Norway enrolled patients.

An independent coordinating center created a treatment-allocation code for each site, labeled vials, monitored compliance

with the blinding procedures, audited the data for consistency and accuracy, and conducted the interim analysis. The full randomization codes remained concealed until completion of the primary analysis.

Treatment

HA-1A (Centoxin; Centocor, Malvern, PA) is a human IgM monoclonal antibody that binds to the lipid A domain of endotoxin and is produced by the stable heteromyeloma cell line A6(H4C5), developed by Teng et al. [19]. This hybridoma was created by fusion of a murine-human heteromyeloma line with splenic B lymphocytes sensitized in vivo by immunization with killed *E. coli* J5 cells and subsequently transformed in vitro by Epstein-Barr virus. The clone produces only human IgM antibody and is free of Epstein-Barr viral genome and of detectable murine viruses. In experimental models, HA-1A protects animals against endotoxemia and development of the dermal Shwartzman reaction [19, 20]. HA-1A has been shown to bind *N. meningitidis* LPS [21]. Clinical studies reported no severe side effects; antibodies to HA-1A were not detected in any patient.

Patients enrolled in this trial were randomly assigned to receive either HA-1A (6 mg/kg bw [1.2 mL/kg bw], with a maximum of 100 mg iv, diluted with 3.5 g of albumin) or an identical-appearing placebo consisting of 3.5 g of human serum albumin. This material was injected into normal saline (3.0 mL/kg bw; maximum, 50 mL). The final solution was infused over a period of 15–30 minutes through an iv line through which no other drug was currently being infused. The study drug was administered as soon as inclusion criteria were met and informed consent obtained. Decisions regarding the use of antibiotics, steroids, iv fluids, inotropes, and cardiovascular and respiratory support were made at the participating centers and were not dictated by the study protocol.

Evaluation of the Patients

The patients were followed for 56 days or until death. At enrollment, three meningococcal disease severity scores were calculated: the Glasgow meningococcal septicemia prognostic score (including hypotension, defined according to age; T_{delta} [central temperature minus peripheral temperature]; modified coma scale; presence of meningitis; deterioration in last hour; extensive rash; and base deficit) [22], the Leclerc score (including age, presence of meningitis, leukocyte count, platelet count, and serum potassium level) [23], and the Stiehm-Damrosch score (including hypotension, recent onset of petechiae, leukocyte count, erythrocyte sedimentation rate, and presence of leukocytes in CSF) [24].

For every patient a blood culture was performed on admission. If meningitis was suspected, CSF was obtained for culture. For some patients a skin aspirate from a hemorrhagic spot was cultured. Blood was drawn on day 0 for an *N. meningitidis* antigen test and also on day 14 for patients with negative cultures.

Shortly before infusion a clinical evaluation was performed. Information was collected regarding the onset of symptoms, onset of petechiae/ecchymoses, first treatment with antibiotics, and transfer from another hospital. The medical history, including known risk factors for meningococcal disease, was obtained. A baseline physical examination was performed, and a detailed description of the skin hemorrhages was recorded. Vital signs (heart rate, blood pressure, respiratory rate, and temperature) were recorded before, in the middle of, and at the end of infusion of the study material; frequently during the first 24 hours after infusion; and then on days 3, 7, 10, and 14. Routine hematologic and clinical chemistry tests were performed before infusion and on days 1, 3, 5, 7, and 14 or until the values were normal. Blood samples for determination of endotoxin levels were collected preinfusion (within 90 minutes after admission) and then 12 and 24 hours postinfusion from the first 123 patients. Samples for HA-1A antibody assay were collected before and approximately 28 and 56 days after infusion.

Endotoxin Assay

For determination of endotoxin levels, blood was collected in pyrogen-free tubes (Falcon 2063; Becton Dickinson, Lincoln Park, NJ) and immediately immersed in melting ice. Pyrogen-free heparin (Organon Teknika BV, Boxtel, the Netherlands; final concentration, 50 immunizing units per mL of blood) was used for anticoagulation. After centrifugation at 190*g* at 4°C for 10 minutes, platelet-rich plasma was collected, immediately frozen, and stored at −20°C. The endotoxin content was determined by a chromogenic *Limulus* amebocyte assay (Coatest Endotoxin; Chromogenix AB, Mölndal, Sweden). The method has a detection limit in blood of 0.036 endotoxin units (EU)/mL. Each sample was assayed in duplicate, and the results were expressed as the mean.

Results

Study Population

In a 5-year period a total of 269 children were enrolled in the study. Nine centers enrolled between 11 and 57 patients each. Of these centers, 2 in the Netherlands, 3 in Great Britain, and 2 in France enrolled 83% of all patients; the remaining 17 centers enrolled between 1 and 6 patients each. Approximately 55 patients were enrolled each year; most patients were admitted to the hospital in the first and last quarters of the year. Two randomized patients did not receive the study drug. One was a patient who was randomized to the HA-1A group but was not infused because of lack of parental consent. The second patient, who was randomized to the placebo group, died before the placebo could be administered. Of the 267 treated patients, 137 received placebo and 130 received HA-1A.

Table 1. Demographics of the 267 patients with meningococcal septic shock who were randomized to receive HA-1A (monoclonal antibody to endotoxin) or placebo.

Characteristic	No. (%) of patients (or other data), per group	
	Placebo (n = 137)	HA-1A (n = 130)
Sex		
Male	72 (53)	83 (64)
Female	65 (47)	47 (36)
Age (y)		
<1	20 (15)	23 (18)
1–2	33 (24)	22 (17)
>2	84 (61)	85 (65)
Mean ± SD	4.5 ± 4.5	5.1 ± 4.5
Symptom duration (d)		
Mean ± SD	1.0 ± 1.1	0.9 ± 0.8
Median	1	1
Range	0–11	0–6
Weight (kg)		
Mean ± SD	20 ± 14	21 ± 14.4
Median	14	15
Range	6.0–80.0	4.5–61.0
Systolic BP (mm Hg)		
Mean ± SD	91 ± 23	93 ± 22
Median	90	91
Range	34–140	46–156
≤70	27 (20)	20 (15)
>70	106 (77)	107 (82)
Diastolic BP (mm Hg)		
Mean ± SD	47 ± 16	47 ± 15
Median	43	45
Range	20–101	0–96
Heart rate (bpm)		
Mean ± SD	169 ± 32	166 ± 28
Median	171	165
Range	90–242	86–220
Presence of purpura*		
Yes	75 (55)	61 (47)
No	61 (45)	69 (53)
GMSPS		
Mean ± SD	4.9 ± 3.1	4.8 ± 3
Median	4	5
Range	0–13	0–13
Leclerc score		
Mean ± SD	−1 ± 1.1	−0.9 ± 1.2
Median	−1.4	−0.7
Range	−2.4–3.0	−2.4–3.0
Stiehm-Damrosch score		
Mean ± SD	1.6 ± 1	1.6 ± 1
Median	1	2
Range	0–4	0–5

NOTE. BP = blood pressure; bpm = beats per minute; GMSPS = Glasgow meningococcal septicemia prognostic score.

* All patients enrolled presented with petechiae.

Table 1 summarizes patient demographics, clinical variables, and the severity scores according to treatment assignment. The placebo and HA-1A treatment groups were well balanced with respect to clinical, hematologic, biochemical, and coagulation variables. The severity of the disease, as measured by the three severity scores, was similar. For patients with endotoxin measurements, the endotoxin concentrations were well balanced and normalized in 24 hours (table 2). No differences in kinetics were observed between the two treatment groups.

Fifteen patients (seven in the placebo and eight in the HA-1A treatment group) received oral antibiotics on the day before hospital admission. In addition, one HA-1A recipient started receiving oral antibiotics 2 days before admission. Intravenous antibiotics were administered to all patients; 88% received cephalosporins. Antibiotic treatment was judged to be adequate in all patients. The median time interval between the start of administration of intravenous antibiotics and that of study medication was 6.4 hours (25th percentile, 4 hours; 75th percentile, 9.7 hours). Forty patients received study medication ≥12 hours after the start of intravenous antibiotic therapy. For these children informed consent was not obtained directly after admittance because the parents were not present or inclusion criteria were fulfilled only during the course of the disease. Within the first week after admission, 142 patients received oral steroids in a therapeutic dosage: 73 patients in the placebo group and 69 in the HA-1A group. The aggressive treatment of the patients reflected the severity of the disease; 97% of the patients received colloidal fluids and/or blood products and 94% were treated with catecholamines.

Efficacy

Sixty-one, or 23%, of the 269 randomized children died within 28 days after randomization. Intention-to-treat analysis

Table 2. Summary of endotoxin concentrations (endotoxin units/mL) in placebo and HA-1A (monoclonal antibody to endotoxin) recipients.

Variable	Placebo	HA-1A
Preinfusion		
n	61	62
Mean ± SD	13.43 ± 28.13	6.13 ± 11.30
Median	2.75	2.73
Range	0.0–120.0	0.0–76.0
12 h Postinfusion		
n	60	61
Mean ± SD	2.99 ± 10.34	1.77 ± 3.74
Median	0.51	0.63
Range	0.0–78.8	0.0–24.39
24 h Postinfusion		
n	57	61
Mean ± SD	0.83 ± 2.21	0.63 ± 2.02
Median	0.18	0.23
Range	0.0–12.0	0.0–15.8
Maximum decrease		
n	58	59
Mean ± SD	9.66 ± 23.44	4.46 ± 6.79
Median	1.92	1.76
Range	0.0–118.31	0.0–39.56
P value		0.9

Table 3. All-cause mortality, overall and in each treatment group.

Variable	Total	Placebo	HA-1A
28-d Mortality			
No. of treated patients	267	137	130
No. (%) of deaths	61 (22.8)	37 (27.0)	24 (18.5)
Reduction (%) vs. placebo group			32
P value* vs. placebo group			.08
Relative risk			0.68
95% CI			0.42–1.10
56-d Mortality			
No. of treated patients	266	136	130
No. (%) of deaths	62 (23.3)	37 (27.2)	25 (19.2)
Reduction (%) vs. placebo group			29.3
P value* vs. placebo group			.15

* Per Fisher's exact test.

showed a mortality of 38/138 (28%) among the placebo-treated patients and 24/131 (18%) in the HA-1A-treated group, resulting in an observed 33% reduction in mortality ($P = .11$, per Fisher's exact test, two-tailed; OR = 0.59; 95% CI for the difference, 0.31–1.05). No relationship between the relative risk (HA-1A vs. placebo) and the size of the treatment site could be demonstrated, and pooled estimates for the small treatment sites were almost the same as the pooled estimates for the large sites (data not shown).

All-cause mortality for patients who were randomized and received the study agent was determined on days 28 and 56; the results are presented in table 3. By 28 days after infusion there were 37 deaths among the 137 placebo recipients (27%) and 24 deaths among the 130 recipients of HA-1A (18%). This 32% reduction in mortality observed on day 28 ($P = .08$) was evident as early as the first 48 hours after treatment. Most deaths (82%) occurred within the first 2 days after randomization. The reduction in mortality was maintained through 56 days, with a 29% overall decrease in deaths from the 27% (37/136) in the placebo group to the 19% (25/130) in the HA-1A group ($P = .15$). For the treated population, the result of a test of homogeneity of the relative odds was nonsignificant ($P = .22$), that is, there was no relationship between size and treatment effect. The observed relative risk for HA-1A was lower for younger children (<1 year [$n = 43$], RR = 0.43; 1–2 years [$n = 55$], RR = 0.75; >2 years [$n = 170$], RR = 0.75), but the difference is fully consistent with chance ($P = .57$). One placebo recipient was lost to follow-up between day 28 and day 56.

Logistic regression explored whether endotoxin concentration predicted outcome for patients treated with antibody to endotoxin. Adjusting for endotoxin concentration did not affect the estimated odds ratio for treatment (table 4). In addition, no difference could be demonstrated after adjustment for age, duration of symptoms, weight, severity scores, blood pressure, and heart rate.

Bacteriology

For four (1.5%) of the patients enrolled, a non–*N. meningitidis* bacterial etiology was documented at initial presentation, but for 199 (74.5%) of the patients either a culture or an antigen test was positive for *N. meningitidis*. Of these 199 patients, 187 had a positive culture of blood, CSF, or skin aspirate; 12 had a positive *N. meningitidis* antigen test. Of the 187 patients with a positive culture, 153 had a positive blood culture (i.e., had documented gram-negative bacteremia). In 64 patients no *N. meningitidis* could be documented by culture or antigen test; 30 patients had a negative culture but no antigen test was performed. Most of these patients (85%) received an antibiotic loading dose before they were transferred to the study hospital and consequently had a negative culture at presentation.

Mortality reduction was consistent across all groups, with *N. meningitidis* documented by a positive culture or antigen test, and regardless of the source of the bacteria (blood [or blood and other sources], CSF, or aspirates). The difference between the placebo and HA-1A treatment groups was not statistically significant in any of these patient subgroups. The 28-day mortality rate for patients with culture- or antigen-proven MSS was 24% among patients receiving placebo and 19% among those who received HA-1A ($P = .49$). HA-1A treatment was not associated with increased mortality in the group with a non-*N. meningitidis* bacterial etiology (one of two patients died in each treatment group). In the group without documentation of meningococcal etiology, the observed mortality was lower for the HA-1A recipients (5/34, vs. 11/30 for placebo recipients).

Sequelae

Sequelae at day 28 included amputation of extremities, skin grafts, presence of neurological sequelae (seizures after day 7, cranial nerve palsies, hemiplegia, hydrocephalus, persistent alteration of level of consciousness), deafness, blindness, and

Table 4. Additional logistic regressions of 28-day all-cause mortality for patients treated with HA-1A.

Logistic regression model	*n*	OR	95% CI
Unadjusted	267	0.61	0.34–1.09
Adjusted for			
Log_{10} (endotoxin)*	213	0.65	0.31–1.37
Documentation of meningococcal or nonmeningococcal disease, culture status	267	0.60	0.34–1.08
Age, duration of symptoms, weight, scores,† purpura, DBP, SBP, heart rate	258	0.66	0.31–1.40

NOTE. DBP = diastolic blood pressure; SBP = systolic blood pressure.

* Models were run with an interaction between treatment and log_{10} (endotoxin); the interaction was not significant at the 0.05 level.

† Glasgow meningococcal septicemia prognostic score, Leclerc score, and Stiehm-Damrosch score.

presence of pericarditis and/or myocarditis. Table 5 presents the frequency of these sequelae separately and in relation to death. The percentage of patients who died or had sequelae was the same in both groups (34% of placebo-treated patients and 33% of HA-1A-treated patients). Sequelae were few in number, ranging from 0.4% (pericarditis) to 5% (surgical procedures performed for complications). Twenty-nine patients (11%) survived with sequelae: 19 (15%) in the HA-1A-treated group and 10 (7%) in the placebo group.

Table 5. Frequency of procedures and sequelae overall and in each treatment group.

	No. (%) of patients		
	Total (n = 267)	Placebo (n = 137)	HA-1A (n = 130)
Procedure			
Surgery	14 (5.2)	6 (4.4)	8 (6.2)
Amputation	11 (4.1)	6 (4.4)	5 (3.8)
Skin graft	9 (3.4)	5 (3.6)	4 (3.1)
Sequela			
Stupor	11 (4.1)	5 (3.6)	6 (4.6)
Coma	9 (3.4)	3 (2.2)	6 (4.6)
Blindness	5 (1.9)	0 (0.0)	5 (3.8)
Hemiplegia	4 (1.5)	2 (1.5)	2 (1.5)
Deafness	3 (1.1)	0 (0.0)	3 (2.3)
Hydrocephalus	3 (1.1)	0 (0.0)	3 (2.3)
Cranial nerve lesion	3 (1.1)	0 (0.0)	3 (2.3)
Myocarditis	3 (1.1)	1 (0.7)	2 (1.5)
Pericarditis	1 (0.4)	0 (0.0)	1 (0.8)
Totals for sequela(e) and/or death			
Either	90 (33.7)	47 (34.3)	43 (33.1)
Both	9 (3.4)	4 (2.9)	5 (3.8)
Death only	52 (19.5)	33 (24.1)	19 (14.6)
Sequela(e) only	29 (10.9)	10 (7.3)	19 (14.6)

Safety

The investigators reported 25 patients who experienced adverse events considered plausibly related to the study agent. The overall rates were 9.5% in the placebo group and 9.2% in the HA-1A group. The most common adverse event associated with the study agent was hypotension, reported in four patients (2.9%) in the placebo group and three (2.3%) in the HA-1A group. Adverse events possibly representing hypersensitivity or allergic reactions (e.g., fever, rash, anaphylactic shock, tachycardia, tachypnea, and urticaria) occurred at similar, low rates (<2%) in both treatment groups. Ten patients had serious, life-threatening, or fatal adverse events that were considered reasonably related to the study agent; six (4.4%) occurred in the placebo group and four (3.1%) in the HA-1A group.

Discussion

In this randomized, placebo-controlled, sequential trial, no statistically significant benefit of HA-1A, a human monoclonal antibody to endotoxin, could be demonstrated in terms of the 28-day mortality for children with MSS. Intention-to-treat analysis showed mortality rates of 28% in the placebo group and 18% in the HA-1A group, for a 33% absolute reduction in mortality (P = .11). The two treatment groups were well matched with respect to demographics, risk factors at presentation, and therapy given for the sepsis syndrome.

At present no single endotoxin-antibody therapeutic strategy has been shown to improve the clinical outcome for patients with sepsis syndrome or septic shock. Nevertheless, in some clinical trials certain subgroups seemed to benefit from endotoxin-antibody therapy. HA-1A has been studied in two large trials. In a multicenter, double-blind, randomized, placebo-controlled phase III trial that included 543 patients with sepsis, no overall benefit of HA-1A could be demonstrated [12]; however, among 102 patients with gram-negative bacteremia and shock, the 28-day all-cause mortality rate was significantly reduced from 56% among patients receiving placebo to 33% among those receiving HA-1A. These results were not confirmed in a second study, a large, group-sequential, placebo-controlled trial that enrolled 2,199 patients, of whom 621 (28%) had gram-negative bacteremia [13].

This latter trial was discontinued at the first interim analysis because the all-cause mortality rate for patients treated with HA-1A who did not have gram-negative bacteremia (42%) exceeded that of patients given placebo (37%) by an amount greater than prespecified in the safety stopping rule. The overall mortality was 33% among patients with gram-negative bacteremia who received HA-1A and 32% in the placebo group.

Several factors can account for the fact that the study showed a lack of overall clinical benefit of HA-1A. First, patients dying of endotoxemia are most likely to benefit from endotoxin-antibody therapy, but until now it has been impossible to clinically identify patients with gram-negative bacteremia and/or endotoxemia in an early stage of the sepsis syndrome. Consequently, these trials in septic patients have shown multiple causative microorganisms (gram-negative and gram-positive bacteria, fungi, etc.) and large differences in the incidence of endotoxemia. Second, the patient populations are often heterogeneous, with multiple risk factors and various concurrent underlying conditions such as cancer, diabetes, trauma, and surgical procedures. The approach of attempting downregulation of the endotoxin-induced pathway of gram-negative sepsis may in fact be valid, but perhaps inadequacies in clinical trial design and/or the anti-endotoxin agents tested have obscured the findings. Further clinical trials should aim to identify a restricted and homogenous patient population that might benefit from therapy.

MSS is a unique model for the study of sepsis because it is a fulminant disease with a specific cause and is rapidly recognizable, owing to its characteristic skin hemorrhages [25, 26]. Moreover, most patients have no underlying disease or specific risk factor present. The high initial endotoxin levels

and the association of these levels with mortality justify attempting endotoxin-antibody therapy in these patients. The present trial is the largest placebo-controlled trial yet undertaken in children with meningococcal sepsis. The finding that for patients receiving HA-1A the observed mortality rate was 32% lower than that for the placebo group but did not reach statistical significance may have a number of possible interpretations.

There may have been a genuine beneficial effect associated with HA-1A that was dampened by nonoptimal timing of intervention. Endotoxin-antibody therapy is expected to work optimally when endotoxin is liberated either by growing bacteria or by treatment with antibiotics. The high initial endotoxin levels in these patients demand immediate treatment, which is not always possible in a clinical trial. Moreover, sepsis is a complex and multifactorial process; once circulating endotoxin has initiated the cytokine cascade, it may be unrealistic to expect that any single therapeutic intervention directed at only one stage will show an important clinical effect.

Although sequelae occurred infrequently, nearly twice as many patients survived with sequelae in the HA-1A-treated group (14.6%) than in the placebo-treated group (7.3%). This may reflect the tendency of HA-1A therapy to keep alive patients who otherwise would have died. However, this result was not statistically significant, and this finding may simply be a result of chance. For a difference of the magnitude observed in the present study to be statistically significant, we would need a trial involving >700 patients. Future trials of immunotherapy in meningococcal sepsis should anticipate mortality rates lower than that reported in the literature, because of earlier referral, improvements in intensive care, and the fact that centers participating in trials have become more experienced in the management of the disease.

A second possible explanation for these results is that HA-1A is not of benefit and the observed nonsignificant reduction in mortality is simply a chance finding. Since the commencement of this trial, conflicting in vitro data have been reported concerning binding of this antibody to LPS and effectiveness in blocking meningococcally induced inflammation [27]. If HA-1A is not a highly active endotoxin-neutralizing agent, the failure to detect a clinical beneficial effect in this trial should not indicate a failure of the principle of endotoxin-antibody therapy but may indicate that HA-1A was not the best anti-endotoxin agent to use in clinical trials.

In summary, HA-1A was chosen for this trial because in MSS, a highly fatal disease, initial plasma endotoxin levels are often extremely high and related to clinical outcome. In this study we could not demonstrate a significant benefit of HA-1A treatment in terms of reduction of mortality among children with MSS. Although endotoxin probably contributes to the development of shock in *N. meningitidis* bacteremia, its potential as a therapeutic target during septic shock remains to be elucidated unequivocally in future trials. The design of the present trial, with a large sample size, is a suitable model for the evaluation of new therapies for meningococcal sepsis.

Appendix

The following institutions and investigators participated in the study.

Steering Committee: P. Brandtzaeg, M.D., Ph.D.; H.H.F. Derkx, M.D., Ph.D. (president); R. de Groot, M.D., Ph.D.; F. Leclerc, M.D.; M. Levin, FRCP, Ph.D.; and A.P.J. Thomson, M.D.

Safety and Monitoring Committee: R. Cunnion (chair), National Institutes of Health, Bethesda, MD; K.K.G. Lan, formerly of the Biostatistics Center, George Washington University, Rockville, MD, and currently of Pfizer, Inc., Groton, CT; C.M. Hamilton, Washington National Cathedral, Washington, DC; L. Lewis, National Cancer Institute, Bethesda, MD; and W. Rodriguez, Children's National Medical Center, Washington, DC.

Coordinating and Data Management Center: Statistics Collaborative, Washington, DC (J. Wittes, Ph.D., and J. Palensky).

Participating centers (the number of patients contributed and the names of investigators follow the name of each center): Imperial College School of Medicine at St. Mary's Hospital, Department of Paediatrics, London, United Kingdom (57; M. Levin, S. Nadel, and I. Maconchie); Sophia Children's Hospital, Rotterdam, the Netherlands (56; R. de Groot, J. A. Hazelzet, and E. van der Voort); Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Amsterdam, the Netherlands (42; B. Derkx, R.P.G.M. Bijlmer, and J. van den Hoek); Institute of Child Health (A.P.J. Thomson, F.A. Riordan, and P. Baines), Royal Liverpool Children's Hospital, Alder Hey (J. Sills and J. Ratcliff), and Royal Liverpool Hospital, Department of Microbiology, Liverpool (C.A. Hart), UK (24); Centre Hospitalier Regional de Lille, Service de Réanimation infantile, Lille, France (21; F. Leclerc, V. Flurin, and C. Fourier); East Birmingham Hospital, Department of Paediatrics and Child Health, Birmingham, UK (12; M. Tarlow); Hôpital Edouard Herriot, Service Réanimation Pédiatrique, Lyon, France (11; D. Floret); CHU de Grenoble, Unité de Réanimation Infantile, Grenoble, France (6; P. Frappat); Hospital Infantil "La Paz," UCI Pediatria, Madrid, Spain (5; F. Ruza Tarrío); Hospital Infantil "Vall d'Hebrón," UCI Pediatría, Barcelona, Spain (5; J. Iglesias Berengue); Academical Hospital Maastricht, Department of Paediatrics, Maastricht, the Netherlands (4; G. Vos); Hôpital de Hautepierre, Service de Pédiatrie I, Strasbourg, France (4; U. Simeoni); Hospital Xeral de Galicia, UCI Pediatria, Santiago de Compostela, Spain (3; J. Martinón Sanchez); CHU Amiens Nord, Service de Pédiatrie II, Amiens, France (3; G. Krim); CHU Saint-Jacques, Service de Réanimation Pédiatrique, Besançon, France (2; A. Menget); Royal United Hospital, Department of Paediatrics, Bath, UK (2; P. Rudd); Department of Clinical Chemistry, Ulleval University Hospital, Oslo, Norway (1; P. Brandtzaeg); Hôpital Robert-Debré, Service de Réanimation Pédiatrique, Paris, France (1; J.C. Mercier); Hospital Materno Infantil, UCI Pediatria, Malaga, Spain (1; C. Calvo Macías); CHU-Nord, Réanimation Pédiatrique, Marseilles, France (1; P. Lagier); CHU-de Nantes, Hôpital de la Mère et de l'Enfant, Réanimation Pédiatrique, Nantes, France (1; J.C. Roze); Hôpital d'Enfants de la Timone, Réanimation Pédiatrique, Marseille, France (1; J. Camboulives); Service de Réanimation Pédiatrique, Hôpital Nord, Saint Priest en Jarez, France (1; G. Teyssier); and Hôpital de Bicêtre, Réanimation Polyvalente, Département de Pédiatrique, Le Kremlin-Bicêtre France (1; G. Huault).

References

1. Derkx HHF, van den Hoek J, Redekop WK, Bijlmer RPGM, van Deventer SJH, Bossuyt PMM. Meningococcal disease: a comparison of eight severity scores in 125 children. Intensive Care Med 1996;22:1433–41.

2. Brandtzaeg P, Kierulf P, Gaustad P, et al. Plasma endotoxin as predictor of multiple organ failure and death in systemic meningococcal disease. J Infect Dis 1989;159:195–204.
3. Gårdlund B, Sjölin J, Nilsson A, Roll M, Wickert C-J, Wretlind B. Plasma levels of cytokines in primary septic shock in humans: correlation with disease severity. J Infect Dis 1995;172:294–301.
4. Van Deuren M, van der Ven-Jongekrijg J, Bartelink AKM, van Dalen R, Sauerwijn RW, van der Meer JWM. Correlation between proinflammatory mediators and the severity of disease in meningococcal infections. J Infect Dis 1995;172:433–9.
5. Brandtzaeg P, Kierluft P. Endotoxin and meningococcemia: intravascular inflammation induced by native endotoxin in man. In: Ryan JL, Morrison DC, eds. Bacterial endotoxic lipopolysaccarides. Vol. 2. Boca Raton, Florida: CRC Press, 1992.
6. Cross AS, Opal SM. Endotoxin's role in gram-negative bacterial infection. Curr Opin Infect Dis 1995;8:156–63.
7. Kulsin VA, Zähringer U, Lindner B, et al. Structural characterization of the lipid A component of pathogenic *N. meningitidis*. J Bacteriol 1992; 174:1793–800.
8. Ziegler EJ, McCutchan JA, Fierer J, et al. Treatment of gram-negative bacteremia and shock with human antiserum to a mutant *E. coli*. N Engl J Med 1982;307:1225–30.
9. J5 Study Group. Treatment of severe infectious purpura in children with human plasma from donors immunized with *Escherichia coli* J5: a prospective double-blind study. J Infect Dis 1992;165:695–701.
10. Greenman RL, Schein RMH, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 1991;266:1097–102.
11. Wenzel RP, Bone RC, Fein A, et al. Results of a second double-blind, randomized, controlled trial of anti endotoxin antibody E5 in gram-negative sepsis [abstract no 1170]. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1994:294.
12. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. N Engl J Med 1991;324:429–36.
13. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR, CHESS Trial Study Group. Treatment of septic shock with human monoclonal antibody HA-1A. Ann Intern Med 1994;121:1–5.
14. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley, 1981.
15. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. Controlled Clin Trials 1984;5:348–61.
16. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958;53:457–81.
17. SAS Institute, Inc. SAS, version 6.08. Cary, North Carolina: SAS Institute, 1994.
18. Hintze JL. PASS user's guide. PASS 6.0, power analysis and sample size for Windows. Kaysville, Utah: NCSS, 1996.
19. Teng NNH, Kaplan HS, Hebert JM, et al. Protection against gram-negative bacteremia and endotoxemia with human monoclonal IgM antibodies. Proc Natl Acad Sci USA 1985;2:59–63.
20. Ziegler EJ, Teng NNH, Douglas H, Wunderlich A, Berger HJ, Bolmer SD. Treatment of *Pseudomonas* bacteremia in neutropenic rabbits with human monoclonal IgM antibody against *E. coli* lipid A. Clin Res 1987; 35:619A.
21. Fujihara Y, Lei M, Morrison DC. Characterization of specific binding of a human immunoglobulin M monoclonal antibody to lipopolysaccharide and its lipid A domain. Infect Immun 1993;61:910–8.
22. Thomson AP, Sills JA, Hart CA. Validation of the Glasgow meningococcal septicemia prognostic score: a 10-year retrospective survey. Crit Care Med 1991;19:26–30.
23. Leclerc F, Chenaud M, Delepoulle F, Diependaele JF, Martinot A, Hue V. Prognostic value of C-reactive protein level in severe infectious purpura: a comparison with eight other scores. Crit Care Med 1991;19: 430–2.
24. Stiehm ER, Damrosch DS. Factors in the prognosis of meningococcal infection: review of 63 cases with emphasis on recognition and management of the severely ill patient. J Pediatr 1996;68:457–67.
25. Kirsch EA, Barton RP, Kitchner L, Girgoir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. Pediatr Infect Dis J 1996;15:967–79.
26. Brandtzaeg P. Systemic meningococcal disease: clinical pictures and pathophysiological background. Rev Med Microbiol 1996;7:63–72.
27. Chan B, Kalabalikis P, Klein N, Heyderman R, Levin M. Assessment of the effect of candidate anti-inflammatory treatments on the interaction between meningococci and inflammatory cells in vitro in a whole blood model. Biotherapy 1996;9:221–8.

Hepatosplenic Cat-Scratch Disease in Children: Selected Clinical Features and Treatment

E. Sami Arisoy, Armando G. Correa, Milton L. Wagner, and Sheldon L. Kaplan

From the Departments of Pediatrics and Radiology, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

We reviewed 19 cases of hepatosplenic cat-scratch disease at Texas Children's Hospital (Houston). The range of the patients' ages was 2 years 4 months to 11 years 8 months. The chief complaint was fever for all patients. The duration of fever before diagnosis was 7 to 56 days (mean, 22 days). Abdominal pain was present in 13 patients (68%). Thirteen children were treated with rifampin alone, and three received rifampin therapy plus gentamicin or trimethoprim-sulfamethoxazole. Once rifampin therapy was initiated alone or in combination, improvement was noted within 1 to 5 days (mean, 2.6 days) for patients who had had prolonged fever the duration of which before rifampin therapy averaged 3 weeks. The most common dosage and duration for our patients were 20 mg/[kg · d] every 12 hours and 14 days, respectively. Rifampin should be considered in the initial antimicrobial treatment of hepatosplenic cat-scratch disease.

Cat-scratch disease (CSD) is a well-recognized, benign, self-limited cause of lymphadenitis in immunocompetent children who have had contact with a cat or kitten [1]. Hepatosplenic CSD is a systemic clinical presentation that is often associated with prolonged fever and microabscesses in the liver and/or spleen [1, 2]. Although several cases of children with hepatosplenic CSD have been reported in the English-language literature [3–30], a prospective, controlled study of antimicrobial therapy has not been performed. The largest series in the literature that retrospectively addressed outcome of therapy included 11 children [29].

We report our experience with 19 cases of hepatosplenic CSD in children who received antimicrobial treatment mostly with rifampin and review previously reported cases regarding treatment and outcome to determine if any therapy might be beneficial.

Methods

The protocol for a retrospective analysis of patients with hepatosplenic CSD who were admitted to or evaluated at Texas Children's Hospital, Houston, during 13 years (1 January 1985 to 31 December 1997) was approved by the Institutional Review Board for Human Subject Research, Baylor College of Medicine and Affiliated Hospitals. The patients with CSD were identified through the ICD · 9 · CM Coding System by the medical records department as well as the patient files of the infectious disease service. During the study period, 101 patients had a diagnosis of CSD. The charts of these patients were reviewed. Patients with hepatosplenic CSD were selected from these cases for the study. The following criteria were necessary for inclusion in the study: evidence of hepatic and/or splenic lesions consistent with CSD that was revealed by ultrasound examination or CT; serological findings consistent with CSD; and serologies, cultures, and skin tests negative for other likely causes of the illness.

Thirty patients with a diagnosis of hepatosplenic CSD were identified. Nineteen patients fulfilled the criteria and were included in the study. Two of these patients have been described previously [26]. The other 11 patients did not undergo serological or histopathologic analyses for diagnostic confirmation.

Fever was defined as a body temperature of >38°C. Time to defervescence was based on the time between the initiation of treatment and the onset of clinical abatement of the patient's presenting symptoms and disappearance of fever. Serological testing was performed with an indirect fluorescent antibody (IFA) assay that detects serum antibody to *Bartonella henselae*. The IFA test was performed at the Centers for Disease Control and Prevention by the method of Regnery et al. [31], and seropositivity was indicated by titers of ≥1:64.

Reports on cases of hepatosplenic CSD in the English-language literature were identified through a MEDLINE search. The references of these articles also were reviewed for additional cases.

Results

The demographic, clinical, radiological, and serological features of the 19 patients are shown in tables 1, 2, and 3.

Clinical findings. The age range of the children with hepatosplenic CSD was 2 years 4 months to 11 years 8 months. The mean age of the children was 5 years 5 months. Twelve patients were male. All patients had a history of contact with a cat and/or kitten (younger than 1 year of age). CSD was the

Received 7 July 1998; revised 22 October 1998.

Reprints or correspondence: Dr. Sheldon L. Kaplan, Mail Code: 3-2371, Texas Children's Hospital, 6621 Fannin Street, Houston, Texas 77030 (skaplan@bcm.tmc.edu).

Clinical Infectious Diseases 1999;28:778–84

1058–4838/99/2804–0017$03.00